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Preface

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The fickle heart: uncertainty quantification in cardiac and cardiovascular modelling and simulation

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1. Introduction

Computational models of the heart are being used to inform drug development [1], make clinical decisions [2] and test basic science hypotheses [3]. Developing mathematical and computational models that represent interacting physical mechanisms and that are informed by experimental and clinical data is a key component of this activity [4]. Cardiac models have increased in sophistication to include subcellular, cellular, tissue and organ-scale effects of electrophysiology, mechanics, haemodynamics, perfusion, fibrosis and the autonomic nervous system [2]. As the accuracy, credibility and use of computational models of the heart have developed, more weight is being placed on their predictions to answer basic science questions, evaluate drug cardiotoxicity or inform clinical treatment decisions. However, as models have become more complicated and sophisticated, the impact of inherent biological variability and measurement error in the data used to constrain the model and its parameters can have a greater impact on predictions. This increased uncertainty needs to be examined and quantified to inform clinicians,

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pharmacists or physiologists of how much to rely on a prediction, to quantify confidence in model parameters and to assist model developers in targeting refinements to the models.

Mathematical and computational models of the heart and cardiovascular system are typically systems of nonlinear ordinary differential equations and nonlinear systems of partial differential equations constrained by conservation laws that are solved using numerical techniques, perhaps on a mesh derived from medical images. Many model parameters are difficult or impossible to obtain directly from routine experimental or clinical measurements. This has led to heart models being developed to simulate representative experimental preparations or patients. Model parameters are then inferred from indirect measurements or are obtained from large amounts of data that have been recorded in different laboratories in highly specialized experimental set-ups. In this process, model parameters are fitted to, or set to, mean measurement values and models are deemed validated, or plausible, if predictions then fall within experimental error bars.

Current cardiac models rely on multiple measurements to inform model parameters. These may be recorded from different hearts or come from a single patient. All measurements are subject to variation and uncertainty that is often not reflected in this process, nor are uncertainties in fitted model parameters, assumed model parameters or underlying model assumptions included in the prediction, which tends to give a single answer—providing no context or indication of model confidence to help inform a clinician, pharmacist or basic scientist's decision.

Model calibration and forward predictions from noisy, uncertain and incomplete data are performed regularly in the fields of meteorology, hydrology, cosmology and petroleum engineering and are increasingly being applied to interpreting omics data. However, these approaches have yet to be applied routinely to models of cardiac structure and function.

Meeting this challenge requires an inter-disciplinary and collaborative approach, bringing together researchers with a range of expertise to create the new community that is needed to have a lasting impact on the cardiac modelling field. This special issue comprises papers that address this challenge, and are based on work done during a month-long programme on uncertainty quantification for cardiac models, held during May–June 2019 at the Isaac Newton Institute in Cambridge and entitled 'The fickle heart' [5].

This special issue aims to highlight recent advances and to stimulate future progress in uncertainty quantification for cardiac and cardiovascular models.

The first three papers in this special issue are perspective pieces, which aim to capture the state of the art and to highlight future directions for research. The first of these papers conducts an uncertainty audit of cardiac models [6] highlighting the uncertainties and variabilities that arise at different scales. The second focuses on the importance of 'discrepancy'—quantifiable differences between models and reality, and tests methods which attempt to account for this on the parametrization of ion channel models [7]. The third paper describes how natural variability between individuals can be captured in the creation of virtual patient cohorts [8].

These perspectives are followed by 12 further research papers, which describe recent developments in the use of statistical methods for uncertainty quantification and sensitivity analysis in cardiac and cardiovascular models. The papers are organized by spatial scale, beginning with those focused on uncertainty in models of subcellular signalling mechanisms in myocytes [9] and fibroblasts [10]. The next paper addresses parametrization of ion channel models while accounting for artefacts in voltage-clamp patch clamp experiments [11]. Two papers perform sensitivity analysis of models for intracellular calcium handling [12] and the atrial action potential [13]. Then a paper looks at variability in electrophysiological properties in tissue and how this relates to arrhythmic risk [14]. The next features the application of 'data assimilation' in cardiac tissue modelling—reconstructing a system's dynamics by combining a biophysical simulation with observed data [15]. Two papers examine uncertainty in the context of left ventricular contraction [16,17]. The final three papers develop methods for patient-specific approaches: for afterload modelling [18]; uncertainty in inferring conduction velocity from clinical measurements [19]; and parameter subset reduction for a simplified model of mechanics and haemodynamics [20].

As evidenced by the breadth of applications covered in this special issue, computational cardiac models are being used beyond tools to replicate and rationalize observations and are now being used to formally test hypotheses, identify optimal model structure and inform decisions. These new applications often require not only a prediction but also a realistic measure of confidence in that prediction. To address these new questions will require the adoption of statistical techniques to create and analyse cardiac models to account for and quantify uncertainty as part of best practice in computational cardiac modelling.

Data accessibility. This article has no additional data.

Competing interests. We declare we have no competing interests.

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